hour at room temperature, then washed four times with TTBS. Serum samples were diluted in specimen diluent without azide to normalize titers, and 100 µl was added per well. These plates were incubated one hour at room temperature and then washed four times with TTBS. HRP-conjugated goat anti-human antibody (Jackson ImmunoResearch) was diluted 1:10,000 in specimen diluent without azide and 100 µl was added per well. The plates were again incubated and washed. To develop the color reaction, TMB (Pierce), was added at 100 µl per well and incubated for 15 min prior to the addition of 30 µl of 2 N H_2SO_4 to stop the reaction. The optical density was measured at 450 nm on a Vmax or Spectramax colorimetric plate reader.

B7

REMARKS

A. Communication Under 37 CFR 1.821-825 and Preliminary Amendment

Applicants request entry of this amendment in adherence with 37 C.F.R. 1.821-1.825. This amendment contains no new matter. Attached hereto is a "VERSION WITH MARKINGS TO SHOW CHANGES MADE," which shows the amendments made to each replacement paragraph. The attached pages are entitled

B. Request to Reference Previously Filed Identical Computer Readable Copy According to 37 CFR 1.821(e)

The paper copy of the Sequence Listing in this application (U.S. Application No. 09/724,552) is identical to the computer readable copy of the Sequence listing filed in U.S. Application No. 09/580,019 filed on May 26, 2000. In accordance with 37 CFR 1.821(e), please use the first computer readable form filed in Application No. 09/580,019 as the computer readable form for the instant application. It is understood the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application.

A paper copy of the Sequence Listing is submitted herewith for incorporation into the instant specification.

Applicant believes that no fee is required for submission of this paper. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's

Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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PATENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 7, line 32, has been amended as follows:

Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

The paragraph beginning at page 8, line 5, has been amended as follows:

Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

The paragraph beginning at page 14, line 13, has been amended as follows:

H_2N-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH (SEQ ID NO:42).

The paragraph beginning at page 28, line 14, has been amended as follows:

Some agents for inducing an immune response contain the appropriate epitope for inducing an immune response against amyloid deposits but are too small to be immunogenic. In this situation, a peptide immunogen can be linked to a suitable carrier to

help elicit an immune response. Suitable carriers include serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, or a toxoid from other pathogenic bacteria, such as diphtheria, *E. coli*, cholera, or *H. pylori*, or an attenuated toxin derivative. Other carriers include T-cell epitopes that bind to multiple MHC alleles, e.g., at least 75% of all human MHC alleles. Such carriers are sometimes known in the art as "universal T-cell epitopes." Examples of universal T-cell epitopes include:

Influenza Hemagluttinin: $HA_{307-319}$ PKYVKQNTLKLAT (SEQ ID NO:43)

PADRE (common residues bolded) AKXVAAWTLKAAA (SEQ ID NO:44)

Malaria CS: T3 epitope EKKIAKMEKASSVFNV (SEQ ID NO:45)

Hepatitis B surface antigen: $HBsAg_{19-28}$ FFLLTRILTI (SEQ ID NO:46)

Heat Shock Protein 65: $hsp65_{153-171}$ DQSIGDLIAEAMDKVGNEG (SEQ ID NO:47)

bacille Calmette-Guerin QVHFQPLPPAVVKL (SEQ ID NO:48)

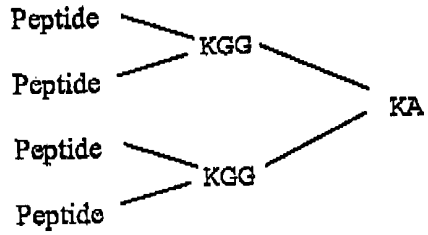
Tetanus toxoid: $TT_{830-844}$ QYIKANSKFIGITEL (SEQ ID NO:49)

Tetanus toxoid: $TT_{947-967}$ FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:50)

HIV gp120 T1: KQIINMWQEVGKAMYA (SEQ ID NO:51).

The paragraph beginning at page 30, line 24, has been amended as follows:

The MAP4 configuration is shown below, where branched structures are produced by initiating peptide synthesis at both the N terminal and side chain amines of lysine. Depending upon the number of times lysine is incorporated into the sequence and allowed to branch, the resulting structure will present multiple N termini. In this example, four identical N termini have been produced on the branched lysine-containing core. Such multiplicity greatly enhances the responsiveness of cognate B cells.



AN90549 (Aβ 1-7/Tetanus toxoid 830-844 in a MAP4 configuration):

DAEFRHDQYIKANSKFIGITEL (SEQ ID NO:52)

AN90550 (Aβ 1-7/Tetanus toxoid 947-967 in a MAP4 configuration):

DAEFRHDFNNFTVSFWLRVPKVSASHLE (SEQ ID NO:53)

AN90542 (Aβ 1-7/Tetanus toxoid 830-844 + 947-967 in a linear configuration):

DAEFRHDQYIKANSKFIGITELFNNFTVSFWLRVPKVSASHLE

(SEQ ID NO:54)

AN90576: (Aβ 3-9)/Tetanus toxoid 830-844 in a MAP4 configuration):

EFRHDSGQYIKANSKFIGITEL (SEQ ID NO:55)

Peptide described in US 5,736,142 (all in linear configurations):

AN90562 (Aβ 1-7/ peptide) AKXVAAWTLKAAADAEFRHD (SEQ ID NO:56)

AN90543 (Aβ1-7 x 3/ peptide): DAEFRHDDAEFRHDDAEFRHDAKXVAAWTLKAAA

(SEQ ID NO:57)

Other examples of fusion proteins (immunogenic epitope of Aβ bolded) include:

AKXVAAWTLKAAA-**DAEFRHD-DAEFRHD-DAEFRHD**

(SEQ ID NO:58)

DAEFRHD-AKXVAAWTLKAAA (SEQ ID NO:59)

DAEFRHD-ISQAVHAAHAEINEAGR (SEQ ID NO:60)

FRHDSGY-ISQAVHAAHAEINEAGR (SEQ ID NO:61)

EFRHDSG-ISQAVHAAHAEINEAGR (SEQ ID NO:62)

PKYVKQNTLKLAT-**DAEFRHD-DAEFRHD-DAEFRHD**

(SEQ ID NO:63)

DAEFRHD-PKYVKQNTLKLAT-**DAEFRHD** (SEQ ID NO:64

DAEFRHD-DAEFRHD-DAEFRHD-PKYVKQNTLKLAT

(SEQ ID NO:65)

DAEFRHD-DAEFRHD-PKYVKQNTLKLAT (SEQ ID NO:66)

DAEFRHD-PKYVKQNTLKLAT-EKKIAKMEKASSVFNV-

QYIKANSKFIGITEL-FNNFTVSFWLRVPKVSASHLE-**DAEFRHD**

(SEQ ID NO:67)

DAEFRHD-DAEFRHD-DAEFRHD-QYIKANSKFIGITEL-

FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:68)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE

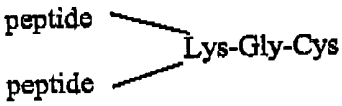
(SEQ ID NO:69)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE-

DAEFRHD (SEQ ID NO:70)

DAEFRHD-QYIKANSKFIGITEL on a 2 branched resin

(SEQ ID NO:77)



EQVTNVGGAISQAVHAAHAEINEAGR (SEQ ID NO:71) (Synuclein fusion protein in MAP-4 configuration).

The paragraph beginning at page 60, line 24, has been amended as follows:

Preparation of coupled Aβ peptides: four human Aβ peptide conjugates (amino acid residues 1-5, 1-12, 13-28, and 33-42, each conjugated to sheep anti-mouse IgG) were prepared by coupling through an artificial cysteine added to the Aβ peptide using the crosslinking reagent sulfo-EMCS. The Aβ peptide derivatives were synthesized with the following final amino acid sequences. In each case, the location of the inserted cysteine residue is indicated by underlining. The Aβ13-28 peptide derivative also had two glycine residues added prior to the carboxyl terminal cysteine as indicated.

Aβ1-12 peptide	NH2-DAEFRHDSGYEVC-COOH (SEQ ID NO:72)
Aβ1-5 peptide	NH2-DAEFRC-COOH (SEQ ID NO:73)
Aβ33-42 peptide	NH2-C-amino-heptanoic acid-GLMVGGVVIA-COOH (SEQ ID NO:74)
Aβ13-28 peptide	Ac-NH-HHQKLVFFAEDVGSNKGGC-COOH (SEQ ID NO:75)

The paragraph beginning at page 102, line 8, has been amended as follows:

The exact array of linear peptides recognized by the antibodies in the serum samples from animals immunized with AN1792 was determined by an ELISA that measured the binding of these antibodies to overlapping peptides that covered the entire Aβ1-42 sequence. Biotinylated peptides with partial sequences of AN1792 were obtained from Chiron Technologies as 10 amino acid peptides with an overlap of 9 residues and a step of one residue per peptide (synthesis No. 5366, No. 5331 and No. 5814). The first 32 peptides (from the eight amino acid position upstream of the N-terminal of AN1792 down to the twenty-fourth amino acid of AN1792) are biotinylated on the C-terminal with a linker of GGK. The last 10 peptides (repeating the thirty-second peptide from the previous series) are biotinylated on the N-terminal with a linker consisting of EGEG (SEQ ID NO:76). The lyophilized biotinylated peptides were dissolved at a concentration of 5 mM in DMSO. These peptide stocks were diluted to 5 μM in TTBS (0.05% Tween 20, 25 mM Tris HCl, 137

mM NaCl, 5.1 mM KCl, pH=7.5). 100 µl aliquots of this 5 µM solution were added in duplicate to streptavidin pre-coated 96-well plates (Pierce). Plates were incubated for one hour at room temperature, then washed four times with TTBS. Serum samples were diluted in specimen diluent without azide to normalize titers, and 100 µl was added per well. These plates were incubated one hour at room temperature and then washed four times with TTBS. HRP-conjugated goat anti-human antibody (Jackson ImmunoResearch) was diluted 1:10,000 in specimen diluent without azide and 100 µl was added per well. The plates were again incubated and washed. To develop the color reaction, TMB (Pierce), was added at 100 µl per well and incubated for 15 min prior to the addition of 30 µl of 2 N H_2SO_4 to stop the reaction. The optical density was measured at 450 nm on a Vmax or Spectramax colorimetric plate reader.